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Original Research

Relationship between thyroid transcription factor 1 and prognosis in locally advanced lung adenocarcinoma

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Abstract

Aim: Stage 3 lung cancers are usually treated with chemoradiotherapy. Thyroid transcription factor 1 (TTF-1) is a transcription protein and TTF-1 is positive in 70% of lung adenocarcinomas. Recent studies have reported that TTF-1 is not only a diagnostic marker but also a prognostic marker. However, to the best of our knowledge, there is no study in the literature showing the relationship between prognosis with TTF-1 in stage 3 patients receiving chemoradiotherapy. For this reason, we retrospectively analyzed the relationship between TTF-1 with prognosis in patients with lung adenocarcinoma who received chemoradiotherapy for the first time in the literature.

Material and Methods: Medical data of 108 patients in Manisa State Hospital between 2009 and 2022 were retrospectively analyzed.

Results: Median overall survival was 32.69 (95% CI, 26.61-38.77) months in the TTF-1 positive group versus 15.28 (95% CI, 11.02-19.54) months in the TTF-1 negative group. Median progression-free survival was 19.68 (95% CI, 16,48-22.88) months in the TTF-1 positive group versus 10.91 (95% CI, 10.08-11.73) months in the TTF-1 negative group. In multivariate analyses, both OS and PFS were associated with ECOG performance score (p= 0.023, p=0.005), TTF-1 (p= 0.001, p= 0.01), stage (p=0.008, p=0.009) and albumin (p=. 0.038, 0.007) level at diagnosis.

Discussion: TTF-1 is both a diagnostic and prognostic marker in lung adenocarcinoma. TTF-1 can be used as an easy and inexpensive biomarker to determine the prognosis in patients receiving chemoradiotherapy diagnosed with stage 3 lung adenocarcinoma.

Keywords

Thyroid Transcription Factor 1, Chemoradiotherapy, Lung Cancer, Prognosis

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Introduction

Lung adenocarcinoma (LAC) is the most common cancer of the lung, accounting for approximately 40% of all lung cancer cases [1]. 40% of patients diagnosed with non-small cell lung cancer (NSCLC) are locally advanced stage III patients [2]. As a standard, surgery is recommended for all eligible patients in the early stage, while cytotoxic chemotherapy, repeated targeted therapy, or immunotherapy is recommended for stage 4 patients. In stage 3 disease, surgery is recommended only in operable stage 3a disease, while chemoradiotherapy is recommended as standard for other stage 3 diseases [3]. Although some clinical and laboratory findings such as age, sex, performance score, albumin, hemoglobin, and lactate dehydrogenase (LDH) levels are associated with prognosis in patients with stage 3 disease, the most important standard prognostic indicator is still stage [4]. Because, even if patients have the same stage, and the same clinical and laboratory findings, they may show different characteristics in daily practice and their prognosis may be different. Therefore, some other prognostic markers are also needed. Thyroid transcription factor 1 (TTF-1) is a transcription protein with both oncogenic and anti-oncogenic properties required for lung differentiation and morphogenesis [5]. It is used in daily routine practice in the diagnosis of lung adenocarcinoma and the differentiation of lung adenocarcinoma from other cancers. TTF-1 is positive in 70% of lung adenocarcinomas [6]. Recent studies have reported that TTF-1 is not only a diagnostic marker but also a prognostic marker. In studies conducted, it has been reported that TTF-1 positive, early-stage, undergoing surgery patients have a better prognosis, and stage 4 patients have better responses to chemotherapy, targeted therapy, and immunotherapy [7-12]. However, to the best of our knowledge, there is no study in the literature showing the relationship between prognosis and TTF-1 in stage 3 patients receiving chemoradiotherapy. For this reason, in our center, we retrospectively analyzed the relationship between TTF-1 with prognosis in patients with lung adenocarcinoma who received chemoradiotherapy for the first time in the literature.

Material and Methods

Study Population

Medical data of 108 patients who received chemoradiotherapy with the diagnosis of stage 3 lung adenocarcinoma in Manisa State Hospital between 2009 and 2022 were retrospectively analyzed. Patients who were 18 years of age or older at the time of diagnosis, had stage 3 disease, were not suitable for surgery, had undergone immunohistochemical staining with TTF-1, and had lung adenocarcinoma histology were included in the study. Patients who were under the age of 18 at the time of diagnosis, did not have lung adenocarcinoma histology, did not undergo immunohistochemical staining with TTF-1, had a stage other than stage 3 or had stage 3 but did not receive chemoradiotherapy, had more than one primary tumor were excluded from the study. The stage of the disease is determined using positron emission computed tomography (PET) and magnetic resonance imaging (MRI).

Data collection

The patients' demographic characteristics such as age and sex, Eastern Cooperative Oncology Group (ECOG) performance scores, smoking history, TTF-1 results, stage and their relationship with survival were examined. The patients were divided into groups according to the Eastern Cooperative Oncology Group (ECOG) performance score (<2 and ≥2), TTF-1 (positive, negative) and stage (3A, 3B). When calculating the survival time, the time from the date of chemotherapy to death or the last follow-up for the patients who survived was calculated. Progression-free survival (PFS) was calculated as the time from the initiation of the first treatment to clinical or radiological progression or to death from any cause for the patients who died. The primary endpoint was PFS and OS, and the secondary endpoint was factors affecting PFS and OS.

Ethical Approval

The study was conducted in accordance with the principles of the Declaration of Helsinki and reviewed and approved by the Health Sciences Ethics Committee of Manisa Celal Bayar University (Decision no: 20.478.486, date: 05/02/2020)

Statistical analysis

Descriptive statistics were presented as mean, standard deviation, median, minimum and maximum values for numerical variables and as numbers and percentages for categorical variables. Survival analyses were performed using the Kaplan-Meier method. Factors affecting survival were examined using the Cox regression. $P < 0.05$ was considered significant in all statistical analyses

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

A total of 108 patients, including 91 (84.3%) males, and 17 (15.7%) females were examined. Their mean age was 63.69 ± 9.61 years. TTF-1 was positive in 76 (% 70.4) patients and TTF-1 was negative in 32 (% 29.6) patients. There were 87 (%80.6) smokers (Table 1). Median cigarettes smoked was 45 (0-150) pack/year. The median albumin level was 3.2 (2.0-4.6) g/dL, the median LDH level was 268 (105-4046) U/L, the median platelet count was 288 (141-585) 103/µL, the median lymphocyte count was 1.7 (0.5-2.8) 103/µL, the median neutrophil count was 5.7 (2.6-1.6) 103/µL and the mean hemoglobin level was 12.66 ± 1.88 g/dL.

The median overall survival was 27.83 (95% CI, 23.67-31.98) months, and the median PFS was 17,08 (95% CI,13.79-20.24) months in all patients.

Stage, ECOG performance score, TTF-1 and albumin level at diagnosis were related to both OS and PFS in univariate and multivariate analyses (Tables 2 and 3)

The survival rates of the patients were respectively 94% at 12 months, 81% at 24 months, 51% at 36 months, 29% at 48 months, and 13% at 60 months in stage 3A disease. In the group with stage 3B disease, the survival rates of the patients were respectively 57% at 12 months, 36% at 24 months, 13% at 36 months, 7% at 48 months, %3 60 months in stage 3B.

The median overall survival was 32.69 (95% CI, 26.61-38.77) months in the TTF-1 positive group versus 15.28 (95% CI, 11.02-19.54) months in the TTF-1 negative group. Median progression-free survival was 19.68 (95% CI, 16,48-22.88) months in the TTF-1 positive group versus 10.91 (95% CI,

10.08-11.73) months in the TTF-1 negative group (Figure 1). During follow-up, after chemoradiotherapy, local recurrence 51 (47.2%), lung metastasis 41 (38%), brain metastasis 19 (17.6%), bone metastasis 37 (34.3%), adrenal metastasis 25 (23.1%), liver metastasis 13 (12%) were detected.

Table 1. Demographic clinical and pathological characteristics of all patients.

Parameters		Number	Percentage (%)
Sex	Male	91	84.3
	Female	17	15.7
Smoker	Positive	87	80.6
	Negative	21	19.4
TTF-1	Positive	76	70.4
	Negative	32	29.6
Stage	3A	36	70.4
	3B	72	66.7
ECOG	<2	87	80.6
	≥2	21	19.4

TTF-1: Thyroid transcription factor 1, ECOG: Eastern Cooperative Oncology Group

Table 2. Correlation between overall survival and clinical factors.

	Univariate analysis (HR, 95% CI)	P value	Multivariate analysis (HR, 95% CI)	p value
Age	1.013 (0.992-1.036)	0.23		
Sex	1.148 (0.860-1.522)	0.37		
Smoking	1.274 (1.015-1.560)	0.045	1.146 (0.895-1.468)	0.28
TTF-1	1.464 (1.174-1.883)	0.008	1.266 (1.076-2.172)	0.01
Stage (3A vs 3B)	2.235 (1.489-2.629)	<0.0001	1.595 (1.066-2.096)	0.009
ECOG	2.048 (1.163-2.607)	<0.0001	1.680 (1.089-1.748)	0.005
BMI	1.011 (0.942-1.085)	0.76		
Albumin	1.732 (1.275- 2.387)	0.001	1.542 (1.125-2.123)	0.007
Hemoglobin	1.039 (0.885- 1.152)	0.89		
LDH	1.000 (0.999-1.000)	0.228		
Platelet	-0.990 (0.998-1.000)	0.225		
Neutrophil	1.000 (1000-1.000)	0.57		
Lymphocyte	1.000 (1000-1.010)	0.19		

HR: hazard ratio, CI: confidence interval, ECOG; Eastern Cooperative Oncology Group, BMI; Body Mass Index, LDH: lactate dehydrogenase

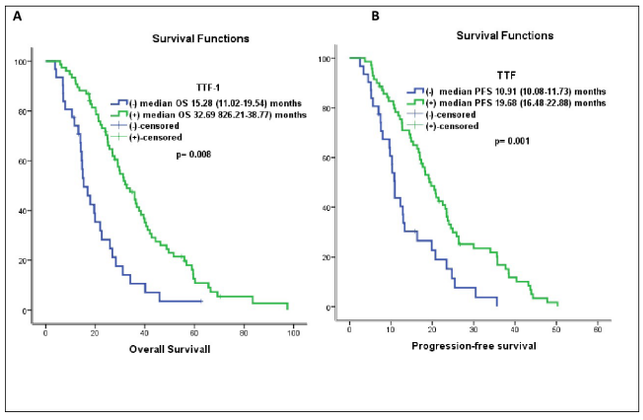

Figure 1. Kaplan-Meier curves of Thyroid transcription factor 1 (TTF-1). A-Overall survival B- Progression-free survival.

Table 3. Correlation between progression-free survival and clinical factors.

	Univariate analysis (HR, 95% CI)	P value	Multivariate analysis (HR, 95% CI)	p value
Age	1.006 80.984-1.018)	0.617		
Sex	1.168 (0.902-1.590)	0.212		
Smoking	1.297 (0.994-1.692)	0.40	1.232 (0.873-1.721)	0.24
TTF-1	1.42 (1.135-1.770)	0.002	1.576 (1.212-2.040)	0.001
Stage (3A vs. 3B)	2.235 (1.489-3.629)	<0.0001	1.805 (1.260-3.205)	0.008
ECOG	2.048 (1.163-3.607)	0.001	1.413 (1.048-1.904)	0.023
BMI	1.011 (0.94-1.085)	0.76		
Albumin	1.332 (1.055-1.681)	0.016	1.332 (1.21-1.706)	0.038
Hemoglobin	1.009 (0.885-1.152)	0.89		
LDH	1.000 (0.999-1.000)	0.228		
Platelet	1.000 (1.000-1.000)	0.57		
Neutrophil	0.999 (0.998-1.000)	0.225		
Lymphocyte	1.000 (0.998-1.001)	0.151		

HR: hazard ratio, CI: confidence interval, ECOG; Eastern Cooperative Oncology Group, BMI; Body Mass Index, LDH: lactate dehydrogenase

Discussion

In this study, we retrospectively examined stage 3 patients who received chemoradiotherapy and we found that prognosis was related to TTF-1, ECOG, stage and albumin level.

According to SEER data, when all lung cancers are considered, the 5-years life expectancy is still around 22.9% [13]. Approximately 15-20% of the patients are in the early stage, 50-60% are metastatic, and the rest are at locally advanced stages [13]. Surgery in the early stages is the standard of systemic treatment in the advanced stages. Chemoradiotherapy is recommended for stage 3A and stage 3 B patients who are not suitable for the operation [3].

Although there was a relationship between stage, albumin, ECOG performance score and the prognosis of patients in previous studies, there is still no standard prognostic marker other than stage in daily practice [4]. In daily practice, patients with similar ECOG scores, albumin levels and stages may have different prognoses. Therefore, there is a need for prognostic markers other than these factors. In our study, unlike the literature, we examined the relationship between TTF-1 with prognosis in patients who received chemoradiotherapy for the first time. As a result of our analysis, we found a significant relationship between TTF-1 with prognosis for the first time in the literature.

TTF-1 is expressed in type II pneumocytes and Clara cells and regulates the surfactant and Clara cell secretory protein gene expression to maintain normal lung functions [14]. TTF-1 is a homeodomain nuclear transcription protein of the NKX2 gene family. By binding to specific gene sequences, TTF-1 modulates the transcriptional activation of target genes [15]. The NKX2–1 locus, which encodes TTF-1, is frequently amplified in the lung cancer genome [15]. TTF-1 could be important for the survival of a subset of patients with lung adenocarcinomas expressing TTF-1 based on the lineage-specific dependency model [16]. Therefore, TTF- 1 may be important in the diagnosis and prognosis of lung adenocarcinoma. In previous meta-analyses, TTF-1 has been reported to be associated with prognosis in

both early and advanced stages [8]. In subsequent studies, TTF-1 has been reported that there may be a relationship between chemotherapy response and TTF-1, and then between targeted therapies with TTF-1 [10-12]. In addition, TTF-1 has recently been reported that TTF-1 positive patients in lung cancer patients receiving immunotherapy have a better prognosis with or without chemotherapy [17-18]. However, this may be due to the fact that TTF-1 inhibits cell migration and invasion, Ki-67 proliferation index is lower in TTF-1 positive patients and EGFR mutations are higher in TTF-1 positive patients, whereas KRAS mutations are more common in TTF-1 negative patients [19-21].

The relationship between radiotherapy and chemoradiotherapy with TTF-1 is unknown. To our knowledge, there is no study examining this relationship. For this reason, we conducted in this study, we found a significant relationship between disease stage, TTF-1, ECOG performance score, with OS and PFS in both univariance and multivariance analysis.

Although the limitations of our study are that it was retrospective, included a small number of patients, and the driver mutations were not known in the patients in the study, this study is important as it is the first study to show the relationship between prognosis and TTF-1 in patients with stage 3 lung adenocarcinoma and receiving chemoradiotherapy at the time of diagnosis.

Conclusion

TTF-1 is both a diagnostic and prognostic marker in lung adenocarcinoma. TTF-1 can be used as an easy and inexpensive biomarker to determine the prognosis in patients receiving chemoradiotherapy with the diagnosis of stage 3 lung adenocarcinoma.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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